REMARKS

Claims 1-67 are currently pending in this application. Claims 20-23 have been rejected and claims 1-19 and 24-67 have been withdrawn from consideration. Applicants have not abandoned the withdrawn subject matter and reserve the right to file one or more divisional applications directed to the withdrawn subject matter if not rejoined.

Claims 20 and 23 have been amended to more particularly recite the claimed subject matter. Support for the amendment appears throughout the specification as filed and in the claims as originally filed.

None of these amendments adds any new matter.

Information Disclosure Statement

The Examiner's consideration of the Information Disclosure Statement filed on May 16, 2005 is acknowledged with appreciation.

Applicants also submit herewith a Second Supplemental Information Disclosure Statement. Applicants respectfully request that the Examiner consider the cited references and return an initialed copy of the PTO-SB-08a/b form with the next Patent Office communication.

Specification (Notice to Comply)

Appropriate correction of the nucleotide sequences contained in the application in accord with 37 C.F.R. §§ 1.821-1.825 is required. Accordingly, Applicants submit herewith an amendment specifically directing entry of the Sequence Listing into the application. The amendment is made to insert the required SEQ ID NO identifiers associated with each listed sequence contained in the Sequence Listing currently on file. The amendments contain no new matter.

Rejections Under 35 U.S.C. § 112

Claims 17-24 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement because, according to the Examiner, "the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possession of the huge genera recited in the claims at the time the application was filed." The Examiner states that the specification

"teaches cDNA encoding parking protein" and is "enabling for a composition comprising a lentiviral vector encoding human parkin protein." Claim 20 also stands rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, "the specification, while being enabling for a composition comprising a lentiviral vector encoding human parkin protein, does not reasonably provide enablement for any other composition comprising a lentiviral vector encoding a parkin protein, a parkin mimetic, a modulator or parkin expression, and a modulator of parkin activity."

In reply, Applicants traverse the rejection. Claim 20 has been amended and is directed to a therapeutic composition, comprising (a) a lentiviral vector comprising a nucleic acid encoding a human parkin protein; and (b) a pharmaceutically-acceptable carrier. A "parkin protein" is defined as having the amino acid sequence set forth in SEQ ID NO:1 in Figure 13 (see paragraph [0038]) of the specification. As further stated in paragraph [0038], parkin includes a parkin peptide and a parkin analogue. Non-limiting examples of parkin peptides are described throughout the specification, for example, at paragraph [0041][00136], and Figures 1 and 9. One of ordinary skill in the art would understand how to prepare a parkin peptide based on the disclosed parkin amino acid sequence (SEQ ID NO:1) and methods for obtaining a parkin proteins disclosed in the specification as filed, for example at paragraphs [0060] and [00127]. A "parkin analogue" is defined in paragraph [0038]. Non-limiting examples of parkin analogs, such as parkin-GST, Flag-parkin, are described throughout the specification, for example at paragraph [00125]. One of skill in the art would understand how to obtain other exemplary parkin analogs, for example, by introducing one or more mutations the parkin amino acid sequence, or a fragment thereof, disclosed in the specification and expressing or synthesizing the mutated parkin amino acid sequence, or fragment thereof, as described in the specification (e.g., at paragraph [0058]) or by methods widely-used in the art.

Based on the above, Applicants submit that present claim 20 is in compliance with the requirements of 35 U.S.C. § 112, first paragraph.

Claims 21 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. The Examiner states that "the specification as filed

fails to disclose that the administration of a lentiviral vector encoding any parkin associated agent...results in the treatment of any neurodegenerative disease."

In reply, Applicants traverse the rejection. The present claims are directed to methods for treating neurodegeneration in a subject comprising administering to the subject a therapeutic composition, comprising (a) a lentiviral vector comprising a nucleic acid encoding a human parkin protein; and (b) a pharmaceutically-acceptable carrier in an amount effective to treat the neurodegeneration in the subject. The specification provides examples of studies conducted using a kainate model of neurodegeneration (for example at paragraphs [00153] – [00156] and [00160]). Kainate (or kainic acid) is used in cell and animal models of neurodegeneration (for a review, see Wang et al. (2005) "Kainic acid-mediated excitotoxicity as a model for neurodegeneration" *Molecular Neurobiology* 31:3-16 (see especially Abstract and Introduction), including Parkinson's disease (Foster et al. (2003) "Kainic acid lesion-induced nigral neuronal death" *J Chem Neuroanat* 26:65-73; Kryzhanovskii et al. (1987) [Modelling of the parkinsonian syndrome by the administration of kainic acid into the caudate nucleus] [in Russian with English abstract] *Biull Eksp Biol Med* 103:650-653). Wang et al. further summarizes several studies which demonstrate that a therapeutic agent (resveratrol) shown to protect neuronal cells in an *in vitro* kainic acid model system using neuronal cells, is also capable of protecting neuronal cells *in vivo* in kainic acid animal models of neurodegeneration. These studies show that, in the kainic acid model of neurodegeneration, a therapeutic effect demonstrated *in vitro* can be translated to an *in vivo* therapeutic effect. Therefore, Applicants' data from an *in vitro* kainic acid model of neurodegeneration demonstrating a therapeutic effect of a therapeutic composition, comprising (a) a lentiviral vector comprising a nucleic acid encoding a human parkin protein; and (b) a pharmaceutically-acceptable carrier supports claims directed to methods for treating neurodegeneration in a subject comprising administering to the subject the claimed therapeutic composition in an amount effective to treat the neurodegeneration in the subject.

Additionally, one of skill in the art would understand how to administer a lentiviral vector encoding a parkin protein to a subject. The art at the time of filing provides guidance for introducing a therapeutic gene therapy lentiviral vector into, for example, a mammalian brain, including a nonhuman primate brain (Naldini et al. (1996) "Efficient transfer, integration, and sustained long-term expression of the transgene in adult rat brains injected

with lentiviral vector" *Proc Natl Acad Sci USA* 93:11382-11388; Kordower et al. (1999) "Lentiviral gene transfer to the nonhuman primate brain" *Exp Neurol* 160:1-16; Pereira de Almeida et al. (2002) "Lentiviral-mediated delivery of mutant huntingtin in the striatum of rats induces a selective neuropathology modulated by polyglutamine repeat size, huntingtin expression levels, and protein length" *J Neurosci* 22:3473-3483). Animal models are used in preclinical experiments as a means for predicting the effect of a therapeutic composition in humans. Indeed, gene transfer using lentiviral vectors has also been the focus of at least one clinical trial (Levine et al. (2006) "Gene transfer in humans using a conditionally replicating lentiviral vector" *Proc Natl Acad Sci USA* 103:17372-17377). Thus, the art at the time of filing teaches one of ordinary skill in the art how to make and use the invention, i.e. how to administer a lentiviral vector to a subject.

The Examiner states that Parkinson's disease (PD) is a multifactorial disease that provides "challenging problems for geneticists because most cases are believed to result form the combined action of multiple genes and environmental factors such as diet, toxins and exposure to drugs." The Examiner further states that "identifying the molecular determinants involved in PD without any a priori knowledge of the mechanism of neurodegeneration is significantly hindered due to the lack of a definitive model system." Applicants submit that there are several useful PD animal models currently widely used by those skilled in the art, including the MPTP model (Smeyne and Jackson-Lewis (2005) "The MPTP model of Parkinson's disease" *Brain Res Mol Brain Res* 134:57-66), the kainate model (Foster et al. (2003) "Kainic acid lesion-induced nigral neuronal death" *J Chem Neuroanat* 26:65-73), and the 6-OHDA model (Deumens et al. (2002) "Modeling Parkinson's disease in rats: an evaluation of 6-OHDA lesions of the nigrostriatal pathway" *Exp Neurol* 175:303-317). Additionally, Applicants submit that it is not necessary to know the underlying molecular determinants of a disorder in order to develop a method for treating the disorder. For example, aspirin was discovered as a painkiller in the late 1800s, but its mechanism of action was not elucidated until 1971.

Applicants submit that the specification and present claims satisfy the requirements of 35 U.S.C. § 112, first paragraph.

Claims 20 and 23 stand rejected under 35 U.S.C. § 112, second paragraph. In reply, Applicants have amended the claims and submit that the present claims satisfy the requirements of 35 U.S.C. § 112, second paragraph.

Claim 23 stands rejected under 35 U.S.C. § 101. In reply, Applicants have amended the claims and submit that the present claims satisfy the requirements of 35 U.S.C. § 101.

Accordingly, applicants respectfully request withdrawal of the rejections under 35 U.S.C. §§ 112 and 101.

Rejections Under 35 U.S.C. § 102

Claim 20 stands rejected under 35 U.S.C. § 102(a) as being anticipated by Bianco et al. (PNAS 99(16):10813-10808 (2002)). The Examiner states that "the scope of the instant claims encompasses a lentiviral vector encoding the parkin-associated agent" and Bianco et al. "teaches a lentiviral vector encoding the α-synuclein protein."

In reply, Applicants traverse the rejection. Applicants submit that Bianco et al. do not disclose every element of claim 20 because the present claim is directed to a therapeutic composition, comprising (a) a lentiviral vector comprising a nucleic acid encoding a human parkin protein; and (b) a pharmaceutically-acceptable carrier. Bianco et al. do not disclose a lentiviral vector comprising a nucleic acid encoding a human parkin protein as required by claim 20. Because Bianco et al. do not disclose every element of the present claim 20, the reference does not anticipate the invention.

Claim 20 also stands rejected under 35 U.S.C. § 102(e) as being anticipated by Kingsman (US 2003/0180740). The Examiner states that Kingsman "teaches a lentiviral vector encoding the parkin protein."

In reply, Applicants traverse the rejection. "In order to anticipate, a prior art disclosure must also be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation." *Novo Nordisk Pharmaceuticals, Inc. v. Bio-technology General Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005) (citing *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1342 (Fed. Cir. 2005)). "The standard for enablement of a prior art reference for purposes of enablement under [35 U.S.C. § 102] differs from the enablement standard under 35 U.S.C. § 112." *Novo Nordisk Pharmaceuticals*, 424 F.3d at

1355 (citing *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005)). According to the Federal Circuit, the "critical inquiry" is whether the prior art discloses in an enabling manner the production of the claimed subject matter. *See Novo Nordisk Pharmaceuticals*, 424 F.3d at 1356 ("The critical inquiry is whether the 1981 Pavlakis article discloses in an enabling manner the production of ripe hGH."). A prior art reference discloses the production of the claimed subject matter in an enabling manner if it discusses particular materials and a particular methodology to produce the claimed subject matter. *See Novo Nordisk Pharmaceuticals*, 424 F.3d at 1356 ("The 1981 Pavlakis article discloses the production of ripe hGH protein in an enabling manner because it discusses particular materials and a particular methodology (the secretion approach) to produce the hGH protein.").

Applicants submit that Kingsman does not disclose in an enabling manner production of a therapeutic composition, comprising (a) a lentiviral vector comprising a nucleic acid encoding a human parkin protein; and (b) a pharmaceutically-acceptable carrier. Kingsman does not disclose *particular* materials and a *particular* methodology to produce the subject matter of the claim. There are no methods disclosed in Kingsman which are particular to parkin, nor is there any disclosure of materials which are particular to parkin. Indeed, the *only* discussion of parkin in the Kingsman specification, reads as follows:

> "Parkin: protein of unknown function with some homology to ubiquitin at the N-terminus and a RING-finger motif at the C-terminus. Deletions identified in juvenile form of Parkinson's disease." Kingsman, paragraph [0381].

This disclosure is not made in connection with any material or methods. Applicants submit that this disclosure of parkin in the Kingsman specification is insufficient to enable one of ordinary skill in the art at the time the invention was made to produce the composition of claim 20.

The Federal Circuit has further stated that a prior art reference may be enabled by "rel[ying] on standard recombinant DNA techniques that would have been understood by one of ordinary skill in the art at the time of its publication." *Novo Nordisk Pharmaceuticals*, 424 F.3d at 1356. However, reliance on standard recombinant DNA techniques is in connection with the disclosure of the prior art reference. Here, Kingsman does not disclose materials or

methods particular to parkin, therefore there is nothing to which one of ordinary skill in the art could apply standard recombinant DNA techniques known in the art.

Because Kingsman does not disclose the subject matter of claim 20 in an enabling manner, the reference does not anticipate the invention.

Applicants therefore request that the rejections of claim 20 under 35 U.S.C. § 102 be withdrawn.

CONCLUSION

Applicants respectfully request that the Examiner enter the present amendment, consider the foregoing remarks, and allow the pending claims to issue. If the Examiner believes that a telephone interview would help expedite the successful prosecution of the claims, the undersigned would be grateful for the opportunity to discuss any outstanding issues.

The Director is hereby authorized to charge any fees due, or credit any overpayment, to Deposit Account No. 08-0219 under order number 19240-443 US2.

Respectfully submitted,

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